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# Phosphate Functionalized Nonisocyanate Polyurethanes with Bio-origin, Water Solubility and Biodegradability

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Nonisocyanate polyurethanes (NIPUs) are an emerging class of polyurethanes produced by circumventing the use of hazardous isocyanates and phosgene in their synthetic route. In this study, we introduce a novel class of water-soluble/dispersible nonisocyanate polyurethanes (NIPUs) containing phosphate pendant groups, referred to as NIPU phosphate monoesters, by applying green chemistry principles. Linear NIPU polymers with number average molecular weight (Mn) values ranging between 7400-13600 Da and weight average molecular weight (Mw) values between 13900-27800 Da were synthesised by the polymerization of bio-derived cyclic biscarbonates 4,4'-(((furan-2,5-diylbis(methylene)) bis(oxy))bis(methylene)) bis(1,3-dioxolan-2-one) (FuBCC) and bis((2-oxo-1,3-dioxolan-4-yl)methyl) succinate (SuBCC) with 1,5-pentanediamine (Cadaverine) by utilizing green solvents. Subsequent functionalization of the resultant NIPUs via mild and selective phosphorylation using tetrabutylammonium dihydrogenphosphate (TBAP) as a phosphate source delivered NIPU phosphate monoesters displaying upto 50% phosphate functionality as determined by $^{1}$H NMR. Interestingly, these phosphate containing NIPUs were soluble/dispersible in water without the need of any external surfactant/co-solvents and demonstrated inherent aerobic biodegradability (56-75% in 28 days). Furthermore, the NIPU phosphate monoesters exhibited remarkable biocompatibility, showing slight to no growth inhibition of human keratinocyte HaCaT cells at concentrations upto 1 mg/mL. In vitro skin irritation assays on reconstructed human epidermis confirmed their non-skin irritant properties. These NIPU phosphate monoesters also exhibited multifunctional characteristics including oil in water emulsion stabilization ability and antimicrobial activity. This work emphasizes the scope and potential of these bio-derived, non-toxic and biodegradable nonisocyanate polyurethane phosphate monoesters as multifunctional additives in personal care/cosmetic applications.

## Introduction

Polyurethanes (PUs) are highly versatile polymers, known for their diverse properties.[1-3] They come in various forms, such as thermoplastic, thermoset, and elastomer, and find wide-ranging applications in foams, coatings, adhesives, sealants, and fibers. In recent years, their biocompatibility has also led to increasing usage in biomedical,[4] personal care,[5] and cosmetic sectors.[6] Traditional PU synthesis involves the reaction of di-functional or poly-functional hydroxyl monomers (-R-(OH)n) with di-functional or poly-functional isocyanate monomers (-R-(NCO)n) in the presence of catalysts.[1] However, isocyanates and their predecessor, phosgene, are highly toxic, posing environmental and health hazards, making PU production potentially dangerous.[7-9] The moisture-sensitivity of isocyanates adds further challenges during their production, storage, and transportation. Additionally, the presence of residual isocyanates in PUs raises concerns[9-11] about mutagenicity and toxicity, especially for applications in biomedical, personal care, and cosmetics. In response to the increasing emphasis on sustainability and stricter regulations [12-13] on toxic chemicals like isocyanates and phosgene, both industries and academia are actively exploring alternative methods for PU synthesis.

Nonisocyanate polyurethanes (NIPUs)[14-18] represent an emerging class of polyurethanes that are produced by isocyanate- and phosgene- free synthetic routes. The most thoroughly studied synthetic routes for NIPUs are by polyaddition of cyclic bis/multi carbonates and di/multi amines which are safer alternatives to diisocyanates and phosgene.[19-23] In addition, the possibility of utilizing $CO_2$ in the cyclic carbonate monomer synthesis makes this route more attractive. Moreover, the polyaddition reaction is 100% atom economic as no by-products are formed. NIPUs produced through this method possess unique features, including free secondary or primary hydroxyl functional groups in their structure, in addition to urethane groups and are also named polyhydroxyurethanes (PHUs). As a result, they exhibit distinct

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characteristics such as strong adhesion, hydrophilicity, thermal stability, and ease of cross-linking. The post-polymerization modification of these hydroxyl groups opens up the possibility of creating new series of isocyanate-free functionalized PUs with tailored properties.[24] Due to their numerous advantages, extensive academic and industry research is underway to improve the synthesis and sustainability of NIPUs,[25,26] design NIPUs with specific properties, and develop hybrid NIPUs[27] and composites.[28] In the past decade, there has been a surge in studies focusing on using bio-based resources,[29-30] such as vegetable oils,[31-32] algal oils,[33] lignin,[34] polyols,[35] and terpenes,[36] for the synthesis of NIPUs. Majority of the studies on applications of biobased NIPUs have been centred around coatings and adhesives[37-39] and investigations into their mechanical properties. More recently, there is a growing momentum in smart NIPUs with properties like recyclability,[40-42] self-healing,[43-44] and shape memory,[45-46] further expanding the potential applications and versatility of these promising polymeric materials.

Water-soluble/dispersible NIPUs[47] are garnering growing interest as a substitute for water-soluble/dispersible PUs utilized in consumer/personal care and biomedical applications. The water solubility of NIPUs can be tuned by the hydrophilicity of functional groups present in NIPU main chain as well as side chain. Nevertheless, research on this subject remains relatively scarce. One of the most effective methods reported for synthesizing water-soluble NIPUs involved the use of water-soluble, polyethylene glycol (PEG) based bis-cyclic carbonate and JEFFAMINE (PEG-co-PPG).[48] However, in this approach, activated bis(pentafluorophenyl)carbonate monomers were employed, resulting in the production of pentafluorophenol as a by-product during the polymerization process. An alternative method to incorporate hydrophilic functionalities into the NIPU polymer is through post-polymerization functionalization of the hydroxyl groups on the NIPU backbone. Matsukizono and Endo[66] reported a study where they reacted NIPU hydroxyl groups with succinic anhydride, followed by neutralization with sodium bicarbonate, resulting in the formation of water-soluble NIPUs containing sodium carboxylate functionality. In a recent study conducted by our group,[50-51] we successfully synthesized bio-derived NIPUs with secondary (-NH-) or tertiary (-NR-) amine groups in their main-chain, which provided these polymers with excellent water solubility/dispersibility. These newly synthesized NIPUs were also explored for their potential applications in home care, specifically as anti-redepositioning agents and were found to be promising.

In this study, we present the synthesis, characterization, and properties of a novel class of water-soluble/dispersible NIPUs containing phosphate pendant groups, referred to as NIPU phosphate monoesters (Figure 1). Organophosphate esters are commonly used as surfactants/emulsifiers in personal care products due to their gentle nature and compatibility with skin.[52-54] Polymeric phosphate monoesters may offer additional advantages, such as film formation and emulsion stabilization, among others. Phosphorous-containing polymers are also well-known for their biocompatibility and have found widespread applications in various biomedical fields, including dental applications, tissue engineering, and drug delivery.[55-56]

Our group has been focusing on exploring NIPUs derived from biomass-derived platform chemicals, such as 2,5-dihydroxymethylfuran (DHMF) and succinic acid. DHMF can be produced through the hydrogenation of 5-hydroxymethyl furan (HMF), a key platform chemical derived from biomass, or directly from fructose via an integrated process.[57-58] Succinic acid, another promising platform chemical, can be produced through the bio-fermentation of biomass.[59-60] Therefore, in this study, we utilized the bis-cyclic carbonates, FuBCC, and SuBCC, derived from DHMF and succinic acid, respectively, as the monomers (see Scheme 1). To further enhance the bio-content in the NIPUs, we selected commercially available bio-based diamine, cadaverine (1,5-diaminopentane), which is produced from renewable plant raw materials through biotechnological processes.[61] In our quest for sustainable production of NIPUs, we not only focused on using renewable resources but also paid special attention to process conditions during the monomer and polymer synthesis. This involved identifying greener solvents or adopting neat conditions, employing metal-free catalytic conditions, and avoiding the use of stoichiometric amounts of hazardous reagents throughout the synthesis. The newly synthesized phosphate functionalized NIPUs were investigated for their solubility, emulsifying ability and antimicrobial activity and the results were found to be encouraging.

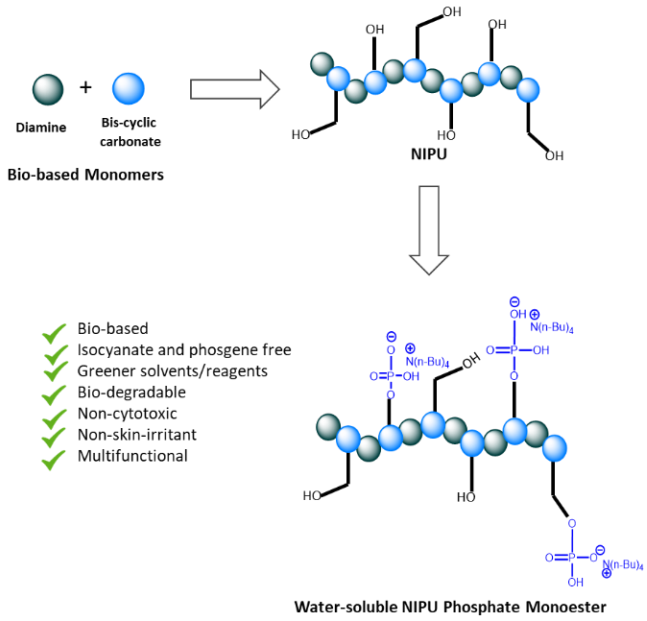


Figure 1: Novel water soluble NIPU phosphate monoesters reported in this work.

Table 1. Alignment of this work to the green chemistry principles and comparison to the state-of-the-art.

| Principles of Green Chemistry[63] | Alignment of this work to Green Chemistry principles |
|---|---|
| 1) Atom economy<br>2) Less hazardous chemical syntheses<br>3) Designing safer chemicals<br>4) Safer solvents and auxiliaries<br>5) Use of renewable feedstocks<br>6) Reduce derivatives<br>7) Catalysis: Catalytic reagents<br>8) Design for degradation<br>9) Inherently safer chemistry for accident prevention | 1) Atom efficient methods with no or only water as the by-product such as $CO_2$ insertion and esterification for the synthesis of monomers (FuBCC and SuBCC) and polyaddition polymerization for the polymers (poly(FuCa) and poly(SuCa)) were adopted.<br>2) The synthesis of FuBCC utilized a metal-free and solvent-free $CO_2$ insertion reaction, while toxic chlorinating agents were avoided during SuBCC production.<br>3) NIPU phosphate monoesters presented in this study were found to be non-skin irritant and non-cytotoxic.<br>4) Although various organic solvents were employed for screening purposes, the final polymerization utilized non-toxic anisole, and the final phosphorylation reaction employed non-toxic γ-valerolactone (GVL).<br>5) Monomers used for the syntheses were biosourced. $CO_2$ was utilized for the synthesis of FuBCC.<br>6) No protecting group chemistry approach was used here<br>7) Metal free catalysis was adopted for the synthesis of the monomers FuBCC and SuBCC.<br>8) Polymers reported here are biodegradable<br>9) NIPU offers a safer alternative to PU because it is manufactured through synthetic methods that eliminate the use of highly toxic isocyanates and phosgene. The synthesis of NIPU phosphate monoesters employed a milder and selective phosphorylation method, using tetrabutylammonium dihydrogenphosphate in conjunction with trichloroacetonitrile, avoiding the need for highly reactive and toxic phosphorylation reagents such as $POCl_3$ and $PCl_3$. |
| Green comparison with the state -of-the-art on water soluble NIPUs | |
| 1) This work avoided fluorinating agents and formation of fluorinated derivatives/ byproducts and employed bioderived monomers unlike the work reported by Sardon et al.[48] | |
| 2) The current work employed non-toxic and environmentally benign solvent anisole for polymerization in contrast to the utilization of DMF for the synthesis of water soluble NIPUs reported by Matsukizono et al.[49] and our earlier work[50]. We have also avoided toxic chlorinating agents for the synthesis of SuBCC distinguishing our approach from that reported by Matsukizono et al.[49] | |
| 3) The polymers reported in this work are biodegradable, non-skin irritant and non-cytotoxic. No other water soluble NIPUs except our previous work[50] reported to have such properties. Moreover, this is the first report of phosphate containing water soluble NIPUs developed for entirely distinct applications and consequently, challenging to draw direct comparisons with previously published research. | |

To the best of our knowledge, this is the first report[62] on phosphate containing nonisocyanate polyurethanes. The syntheses and characteristics of these functional polymers fulfils at least 9 of the 12 green chemistry principles[63] (Table 1) such as the use of less hazardous chemistry, atom economic synthesis, use of renewable feedstock, benign chemicals, solvents, and catalytic routes, which make the whole process and products greener. The *E* factor[64] of individual synthesis steps were calculated, which ranged from 6 – 27 and fell within the accepted range of fine chemicals synthesis.[64] Additionally, the reported water-soluble NIPU phosphate monoesters were demonstrated to be non-cytotoxic, non-skin irritant, and bio-degradable underscoring their potential for various applications such as greener multifunctional ingredients for personal care and cosmetics.

## Experimental

### Materials and Methods

All reagents and solvents were used as received without further purification. Dry solvents (acetonitrile, dimethylformamide (DMF), tetrahydrofuran (THF) and toluene) were drawn from a Glass Contour solvent purification system. Other solvents 2-methyl tetrahydrofuran (2-MeTHF), anisole, cyclopentyl methyl ether (CPME) and γ-valerolactone (GVL) were used as received without further purification. All reactions requiring anhydrous conditions were carried out under argon atmosphere using oven-dried glassware. $^{1}H$, $^{13}C$ and $^{31}P$ NMR spectra were recorded on a Bruker 400 MHz instrument. Chemical shifts for protons were reported in parts per million (ppm) that is referenced to the residual proton peak of the solvent ($CDCl_3$:7.26, DMSO-$d_6$: 2.50). Chemical shifts for carbon were also referenced to the carbon peaks of the solvent ($CDCl_3$: 77.2). Chemical shifts for phosphorus were referenced to external 85% phosphoric acid, which is assigned the chemical shift of zero. The chemical shifts were reported in parts per million (ppm) and multiplets were assigned as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet) and brs (broad singlet). Size-exclusion chromatography (SEC) analysis was carried out on a Waters Binary GPC system with the Waters 2414 refractive index detector. DMF was used as the eluent, with a flow rate of 0.3 mL/min and poly(methylmethacrylate) (PMMA) standards were used for calibration. Aqueous gel permeation chromatography (GPC) was carried out in 0.1 N $NaNO_3$ solution and PEO standards were used for calibration. Thermogravimetric analysis (TGA) spectra of polymers were recorded on a TA Instruments TGA-Q500 with heating rate of 10 °C/min under air. Differential Scanning Calorimetry (DSC) data were recorded on a Mettler Toledo DSC 3 with a heating rate of 10 °C/min under nitrogen. The dynamic light scattering measurements were performed on Malvern Zetasizer nano ZS. The polymer was dispersed in water

to make stable dispersion prior to size and zeta potential measurements at 25 °C. Microscopy images were recorded on a Nikon Eclipse Ci-L microscope system. The viscosities of the polymer solutions were recorded on Anton Paar Rheometer MCR 302 by using a 25 mm parallel plate. Shear rate of 5 – 100 $s^{-1}$ was applied on the samples at 25 °C.

**Synthesis of 2,5-bis((oxiran-2-ylmethoxy)methyl)furan (bisepoxide) (FuBE)**

FuBE was synthesized by a literature method.[65] The product FuBE was obtained as a yellow liquid (30.8 g, yield 80 %).$^1$H NMR (400 MHz, $CDCl_3$) δ 6.29 (s, 2H), 4.53 – 4.43 (m, 4H), 3.76 (dd, *J* = 11.5, 3.1 Hz, 2H), 3.44 (dd, *J* = 11.5, 5.8 Hz, 2H), 3.15 (dd, *J* = 6.3, 3.1 Hz, 2H), 2.79 (t, *J* = 4.6 Hz, 2H), 2.60 (dd, *J* = 5.0, 2.7 Hz, 2H).

**Synthesis of 4,4'-(((furan-2,5-diylbis(methylene)) bis(oxy)) bis(methylene)) bis(1,3-dioxolan-2-one) (FuBCC)**

2,5-bis((oxiran-2-ylmethoxy)methyl)furan (FuBE) (10.8 g, 45.0 mmol) and tetrabutylammonium bromide (TBAB) (0.435 g, 1.35 mmol) were added into a 160 mL Parr reactor with a glass liner. The reactor was purged with $N_2$ followed by $CO_2$ and then pressurized with $CO_2$ up to 20 bar. The reaction was carried out under stirring at 105 °C for 18 h. After the reaction, the reactor was cooled to room temperature and depressurized. The crude product was passed through a pad of silica gel using ethyl acetate: petroleum ether (2:1, 90 mL) as the eluent. The solvent was removed under reduced pressure giving the product FuBCC as a white solid (12.7 g, yield 86%). $^1$H NMR (400 MHz, $CDCl_3$) δ 6.29 (s, 2H), 4.53 – 4.43 (m, 4H), 3.76 (dd, *J* = 11.5, 3.1 Hz, 2H), 3.44 (dd, *J* =11.5, 5.8 Hz, 2H), 3.15 (dd, *J* = 6.3, 3.1 Hz, 2H), 2.79 (t, *J* = 4.6 Hz, 2H), 2.60 (dd, *J* = 5.0, 2.7 Hz, 2H) $^{13}$C NMR ($CDCl_3$, 100 MHz): δ= 151.9, 110.3, 70.8, 65.3, 50.8, 44.3.

**Typical synthesis of bis((2-oxo-1,3-dioxolan-4-yl)methyl) succinate (SuBCC)**

To a suspension of succinic acid (98.0 g, 830 mmol) and glycerol 1, 2-carbonate (200.0 g, 1680 mmol) in toluene (750 mL), *p*-toluene sulfonic acid (2.0 g, 10.5 mmol) was added, and the mixture was heated to reflux for 5 h using a Dean–Stark apparatus. After cooling the reaction mixture to room temperature, toluene was decanted and the residual syrup was dissolved in hot acetone (200 mL), followed by precipitation in ethanol (500 mL) to yield the product SuBCC as a white solid (211 g, yield 80%). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 5.03 (m, 2H), 4.56 (t, 2H), 4.27 (m, 6H), 2.62 (s, 4H). $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 171.69, 154.81, 74.33, 66.04, 63.66, 28.48. Anal. Calcd. (%) for $C_{12}H_{14}O_{10}$: C; 45.29; H, 4.43. Found: C, 45.25; H, 4.50.

**General procedure for polymerization reaction in various solvents (Table 2)**

In a typical experiment, FuBCC (500 mg, 1.52 mmol) and 250 µL of mesitylene (as internal standard) were taken into the glass reactor and the content was dissolved in the respective solvent (1.5 mL) or neat while stirring on an oil bath at 75 °C (oil bath temperature). Once all the biscarbonate was dissolved, cadaverine (155 mg, 1.52 mmol) was charged into the reaction tube to initiate the reaction. Reaction mixture was then allowed to stir for 24 h. Liquid samples were collected at regular intervals of time using a syringe to monitor the monomer conversion using $^1$H NMR spectroscopy. Finally, the reaction mixture was cooled down to room temperature and the polymer was precipitated using excess diethyl ether. The light brown polymer was then dried under air followed by vacuum at 80 °C.

**Typical Synthesis of NIPUs in anisole (Table 2)**

In a typical synthesis of NIPU, FuBCC (10.3 g, 31.5 mmol) or SuBCC (10.0 g, 31.5 mmol) was added into the reactor. The content was dissolved in anisole (30 mL) and the diamine (3.218 g, 31.5 mmol) was added. The reactor was sealed, and the reaction mixture was stirred for 28 h at 70 °C. Finally, the reaction mixture was cooled down to room temperature and the excess anisole was decanted. The polymer was then dissolved in methanol (10 mL) and the polymer was precipitated from diethyl ether (20 mL). The process was repeated two more times. The light brown polymer was dried under air followed by vacuum at 80 °C, giving poly(FuCa) and poly(SuCa) in yields above 90%. Poly(FuCa): $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.10 (br, 2H), 6.38 (br, 2H), 4.99 (br, 1H), 4.79 – 4.70 (br, 1H), 4.69 (br, 1H), 4.40 (br, 4H), 3.91 – 3.73 (br, 3H), 3.53 – 3.38 (br, 6H), 2.95 (br, 4H), 1.38 (br, 4H), 1.24 (br, 2H). Poly(SuCa): $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.15–7.00 (br, 2H), 5.18 (br, 1H), 4.90 (br, 1H), 4.76 (br, 1H), 4.28 – 3.84 (br, 7H), 3.48 (br, 2H), 2.95 (br, 4H), 2.59 (br, 4H), 1.38 (br, 4H), 1.22 (br, 2H).

**Post polymerization functionalization of NIPUs by Phosphorylation**

**Typical Synthesis of Poly(FuCa)-P15**

To a solution of poly(FuCa**)** (10.8 g, 22.7 mmol) in GVL (25 mL), trichloroacetonitrile (TCAN) (1.5 mL, 15 mmol) was added followed by dropwise addition of a solution of tetrabutylammonium dihydrogen phosphate (TBAP) (3.4g, 10 mmol) in anhydrous acetonitrile (10 mL). After the addition, the reaction mixture was allowed to stir for 18 h at 50 °C. Upon completion of the reaction, the solvent was removed to obtain a brown solid. The solid was then dissolved in small amount of methanol (10 mL) and re-precipitated using diethyl ether (50 mL). This step was repeated three times before drying under vacuum to obtain poly(FuCa)-P15 as a brown solid in 80-85% yield.

**Typical synthesis of Poly(FuCa)-P50**

To a solution of poly(FuCa**)** (10.8 g, 22.7 mmol) in GVL (25 mL), TCAN (6 mL, 60 mmol) was added followed by dropwise addition of a solution of TBAP (18.7 g, 55 mmol) in anhydrous acetonitrile (50 mL). After the addition, the reaction mixture was allowed to stir for 18 h at 50 °C. Upon completion of the reaction, the solvent was removed to obtain a brown solid. The solid was then dissolved in small amount of methanol (10 mL) and re-precipitated using diethyl ether (50 mL). This step was repeated three times before drying under vacuum to obtain poly(FuCa)-P50 as a brown solid in 80-85% yield.

**Typical Synthesis of Poly(SuCa)-P15**

To a solution of poly(SuCa) (15.0 g, 36.0 mmol) in GVL (50 mL), TCAN (2.2 mL, 22 mmol) was added followed by dropwise addition of a solution of TBAP (4.75 g, 14 mmol) in anhydrous acetonitrile (10 mL). After the addition, the reaction mixture was stirred at 50 °C for 18 h. Upon completion of the reaction, the solvent was removed to obtain a brown solid. The solid was then dissolved in small amount of methanol (15 mL) and re-precipitated using diethyl ether (75 mL). This step was repeated three times before drying under vacuum to obtain poly(SuCa)-P15 as brown solid in 85% yield.

**Typical synthesis of Poly(SuCa)-P50**

To a solution of poly(SuCa) (1.05 g, 2.5 mmol) in GVL (2.5 mL) at 50 °C, TCAN (0.6 mL, 6.0 mmol) was added followed by dropwise addition of a solution of TBAP (1.87g, 5.5 mmol) in anhydrous acetonitrile (5 mL). After the addition, the reaction mixture was stirred at 50 °C for 18 h. Upon completion of the reaction, the solvent was removed to obtain a brown solid. The solid was then dissolved in small amount of methanol (1 mL) and re-precipitated using diethyl ether (5 mL). This step was repeated three times before drying under vacuum to obtain poly(SuCa)-P50 as a brown solid in 81% yield.

**Solubility Studies**

The NIPU phosphate monoester (0.25 g) was weighed and placed in a glass vial followed by the addition of solvent (2.25 g) at room temperature. The mixture was placed in a water bath (25 °C) and stirred for 2 h at 500 rpm. After that, the stirring was stopped and the solution was rested at room temperature for 18 h. The polymer was considered soluble in the solvent if the solution was clear without polymer residue. The polymer was considered dispersible in the solvent if a milky solution was obtained without polymer residue. Lastly, the polymer was considered non-soluble or partially soluble if polymer residue was spotted at the bottom of glass vial.

**Emulsion Stabilization Studies**

Olive oil (4 g) was weighed in a beaker and heated to 80 °C. A solution of NIPU phosphate monoester (0.2 g) in DI water (35.8 g) was stirred at 80 °C in a separate beaker. The oil was gradually added into the polymer solution while mixing with a homogenizer at 80 °C. After addition, the emulsion was cooled down to room temperature while mixing. The emulsion was left at room temperature for 24 h prior to optical microscopy analysis.

**Antimicrobial activity Test**

The antimicrobial activities of the polymers were measured by cup plate method. This experiment was carried out at Disease Intervention Technology Laboratory, Institute of Molecular and Cellular Biology (IMCB), Agency for Science Technology and Research, Singapore 138648. LB-agar plates were made by pouring 25 ml sterile LB-agar media in 90 mm petri dish, cooled down to room temperature and stored at 4 °C. Three or four cups were bored in each plate using a sterile steel cork borer of 8 mm diameter. The overnight culture of *E. coli* strain K12 or *Bacillus sp.* strain JJ-1b (ATCC 35889) were made in LB broth and diluted to $OD_{600}$ = 1.0, and uniformly spread on the plates using sterile cotton swabs and incubated at room temperature for 1 hour. The cups were filled with the samples (polymer dissolved in DMSO) or the pure solvent and allowed to diffuse at room temperature for 3 h, followed by overnight incubation at 37 °C. Presence of clear zone of inhibition indicates antimicrobial activity of the samples; the diameter of the zone of inhibition was measured to compare the antimicrobial activity of various samples. Images of the plates were captured and pasted on PowerPoint slides, and the zone of inhibitions were measured from the diameter of the circles drawn on the images around the clear zone where microorganisms did not grow.

**Cytotoxicity Test against HaCaT cells**

The cytotoxicity tests of the NIPU phosphate monoesters were carried out in Singapore Polytechnic, Singapore. The polymers were dissolved in DI water at 10 mg/mL. Firstly, HaCaT cells were seeded into 24-well plates at a density of 50,000 cells/well. After 24 h, the medium was replaced with fresh medium containing the polymer samples at various concentrations. The cells were incubated at 37 °C and at 5% $CO_2$ for another 24 h. Following this, 300 µl of CCk-8 kit was added into each well and incubated for another 3.5 h. The absorbance was then measured at 450 nm using Thermo Scientific MultiSkan GO reader. Background wells were treated with equal volumes of growth medium as that of the sample wells but without cells. The inhibitory effect of the samples was measured by comparing the absorbance of the control growth (HaCaT cells grown in culture medium in DI water). All measurements were repeated six times. From there, the percentage of live cells was calculated.

**Skin Irritation Test of Poly(FuCa)P-50 by OECD 439**

The skin irritation test was carried out by Denova Sciences Pte Limited, Singapore for the hazard identification of irritant chemicals. Reconstructed human epidermis (RhE) supplied by EPISKIN were pre-incubated with medium for 24 h. Following exposure of 5 w/w% of poly(FuCa)P-50 solution in DI water for 15 minutes at room temperature and a post-treatment incubation period for 42 h in fresh medium, the cell viability of tissue was measured by using MTT assay. Phosphate buffered saline (PBS) and 0.5% sodium dodecyl sulfate (SDS) were used as negative and positive controls, respectively. At least three replicates were performed for each polymer.

**Biodegradability Test**

The inherent aerobic biodegradability test according to Zahn Wellens Test OECD 302 B was done by Singapore Test Service, Singapore using activated sludge extracted from Jurong water reclamation plant, Singapore as the inoculum. Total organic carbon (by combustion catalytic oxidation technique) was utilized to determine the remaining biodegradable material as organic carbon after 28 days.

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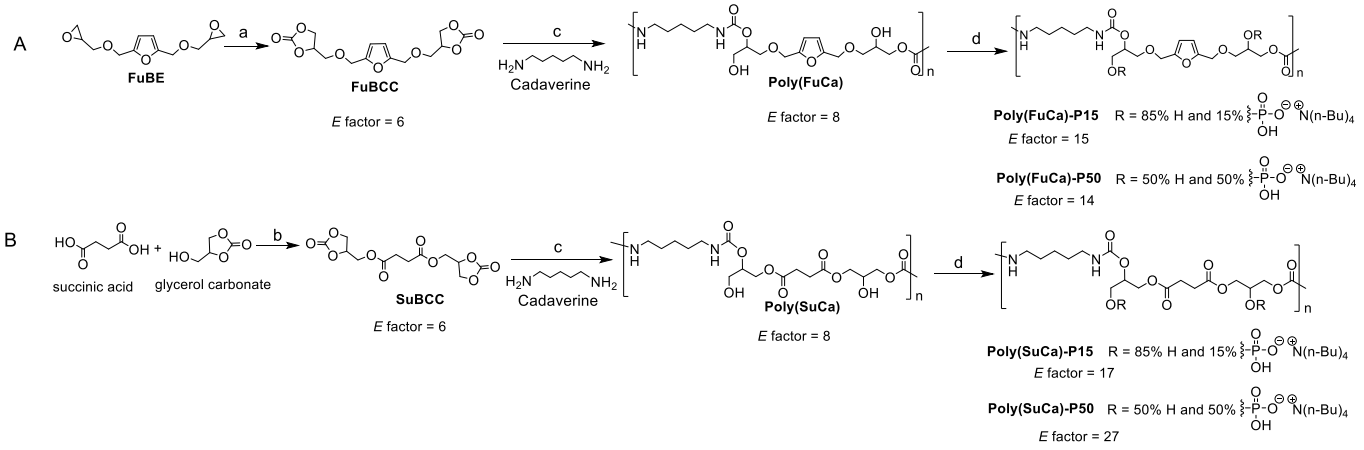


Scheme 1: Synthesis of biobased biscarbonate monomers, biobased NIPUs and NIPU-phosphate monoesters including *E* factor of each step. a) 20 bar $CO_2$, 3 mol% TBAB, neat, 105 °C, 18 h, b) 1 mol% p-TsOH, toluene, 125 °C, 5 h, c) anisole, 70 °C, 28 h, and d) TBAP (0.6 eq dissolved in acetonitrile), TCAN, GVL (50 °C), 18h.

## Results and Discussion

### Synthesis and characterization of biobased cyclic biscarbonates and their NIPUs

The bis-cyclic carbonate, 4,4'-(((furan-2,5-diylbis(methylene)) bis(oxy))bis(methylene)) bis(1,3-dioxolan-2-one) (FuBCC), was synthesized from bisepoxide derivative, 2,5-bis((oxiran-2-ylmethoxy)methyl)furan (FuBE), using an improved method involving $CO_2$ fixation as a crucial step (Scheme 1A). Recently, $CO_2$ insertion into FuBE using a complex lanthanum-based catalyst[8165] containing zwitterionic ligands together with tetrabutylammonium bromide (TBAB) as a co-catalyst was described. In contrast, our approach utilized a simple metal-free system and demonstrated that the $CO_2$ insertion into FuBE proceeded efficiently using only TBAB as the catalyst under solvent-free (neat) conditions at 105°C and 20 bar, resulting in FuBCC monomer yields exceeding 80%.

SuBCC was conventionally synthesized by reacting succinyl chloride with commercially available and bioderived glycerol 1,2-carbonate in chlorinated solvents.[49] Although this method is highly efficient, it necessitates the conversion of carboxylic acid to acid chloride using toxic chlorinating agents such as thionyl chloride, phosgene, or phosphorous pentachloride.[66] A simpler and more environmentally friendly approach for SuBCC synthesis is the direct di-esterification of succinic acid with glycerol 1,2-carbonate.[67] Despite its lower solubility in toluene, we found that di-esterification of succinic acid with glycerol 1,2-carbonate could be effectively achieved under azeotropic distillation conditions using a catalytic amount of p-toluenesulfonic acid (pTsOH), resulting in high yields of SuBCC (Scheme 1B). This process is easily scalable and greener compared to other routes as it only produces water as a by-product, and the solvent toluene can be recycled. In this work, the synthesis of SuBCC was demonstrated at 200 g scale with a yield of 80% by the latter approach.

Subsequently, the polyaddition polymerization of these biobased cyclic carbonates with cadaverine was examined. Owing to the high polarity of the monomers and the hydrogen bonding effects of the hydroxyl groups in the resulting NIPUs, polar solvents like DMF are commonly utilized for the polyaddition polymerization reaction. The selection of solvents holds utmost importance from a green and sustainable manufacturing perspective.[68-69] Moreover, the presence of even trace amounts of toxic solvent impurities in the product could have implications in applications involving human contact, such as in personal care or cosmetics. Consequently, the impact of solvents on the polymerization reaction between FuBCC and cadaverine to form poly(FuCa) was initially investigated with the aim of identifying more environmentally friendly alternatives (Table 2). Polar aprotic solvents DMF and THF, commonly used in such reactions, yielded high conversions (>95%) of FuBCC. The molecular weight of the resulting polymers was determined by size exclusion chromatography (SEC) in DMF using PMMA calibration which indicated number average molecular weight (Mn) values up to 7300 Da and 12000 Da respectively and polydispersity (Đ) ranging between 1.77-1.80 (entries 1-2, Table 2). Considering the known toxicity of DMF[70-71] and the flammability and potential explosive peroxide

formation of THF, we explored other solvent options. Solvents like water, alcohols, esters, ketones, and carbonates were avoided due to their potential reactivity with the cyclic carbonate or diamine monomers. Promisingly, greener solvents such as anisole, CPME and 2-MeTHF,[72-73] were found to be effective despite their relative lower dielectric constants presenting > 95% conversions, Mn values in the range of 10700 to 13700 Da (entries 3-4, Table 1) and Đ values between 1.67 to 2.10. The polymerization reaction also worked under neat conditions; however, the resulting polymer had a lower molecular weight (entry 6, Table 2).

Table 2. Solvent screening for the polymerization of FuBCC and cadaverine [a]

| Entry | Solvent | Dielectric Constant (25 °C) | Mn[b] [Da] | Mw[b] [Da] | Đ |
|---|---|---|---|---|---|
| 1 | DMF | 36.7 | 7 300 | 13 100 | 1.80 |
| 2 | THF | 7.58 | 12 400 | 22 000 | 1.77 |
| 3 | Anisole | 4.33 | 10 700 | 17 700 | 1.67 |
| 4 | 2-MeTHF | 6.97 | 13 200 | 27 800 | 2.10 |
| 5 | CPME | 4.76 | 13700 | 24600 | 1.79 |
| 6 | Nil | - | 5 700 | 11 800 | 2.08 |

a) Reaction conditions: 70 °C, 28 h. b) obtained from SEC (DMF) using PMMA calibration

Accordingly, anisole was chosen as the solvent for the polyaddition polymerization based on its advantageous features, such as being low-cost, non-toxic, non-volatile, and biodegradable, and that it holds a prestigious position in the CHEM21 guide.[73] Thus, two NIPU polymers namely poly(FuCa) and Poly (SuCa) were synthesised by the polymerization of FuBCC and SuBCC with cadaverine in anisole at 70 °C for 28 h in the absence of any catalysts or inert conditions (Scheme 1). $^1$H NMR (Figure 2) and IR (Figure S2 and S4) confirmed the structure of the polymers.

Table 3: Molecular weight and thermal data of the NIPUs synthesised

| Polymer Code[a] | Mn[a] [Da] | Mw[a] [Da] | Đ | Tg [ºC] | $T_{5\%}$ [ºC][b] |
|---|---|---|---|---|---|
| **Poly(FuCa)** | 10700 | 17900 | 1.67 | 8 | 240 |
| **Poly(SuCa)** | 7400 | 14000 | 1.88 | - 6 | 215 |

a) obtained from SEC (DMF) using PMMA calibration b) from TGA in Air

Table 3 presents the molecular weight and thermal data of the NIPUs synthesised. The SEC analysis indicated Mn values ranging between 7400-10700 Da and Mw values between 14000-17900 Da. The Đ values fell within the range of 1.67 to 1.88. Thermal properties were determined using differential scanning calorimetry (DSC) with a heating rate of 10 °C/min under a nitrogen atmosphere, and thermogravimetric analysis (TGA) under air. DSC analysis revealed that both NIPUs exhibited glass transition temperatures (Tg) below room temperature, ranging from -9 to 8 °C. Poly(FuCa) displayed a relatively higher Tg, which can be attributed to its aromatic content. In terms of thermal stability under air, TGA results showed that poly(FuCa) and poly(SuCa) demonstrated good stability with 5% weight loss ($T_{5\%}$) occurring at 240 °C and 215 °C, respectively.

**Synthesis and characterization of NIPU phosphate monoesters**

To achieve mild and selective phosphate functionalization of NIPU hydroxyl pendants while avoiding any crosslinking, we adopted a direct one-pot method utilizing commercially available tetrabutylammonium dihydrogenphosphate (TBAP) as the phosphate source (Scheme 1). The reaction was facilitated by the presence of trichloroacetonitrile (TCAN) as a mild coupling reagent. In addition to the high selectivity towards monoesters, the advantage of this approach also lies in the avoidance of highly reactive and toxic phosphorylation reagents[74] such as phosphorous trichloride, diethylchlorophosphite, and phosphoryl chloride. Originally developed by Cramer and co-workers[75] for monophosphate ester synthesis from terpene alcohols, this methodology was later expanded to various alcohols by other research groups.[76-77] It was proposed that TCAN activated TBAP forming an activated phosphorylated trichloroacetamidate which facilitated nucleophilic attack of the hydroxyl groups forming the corresponding phosphate esters.[76-77]

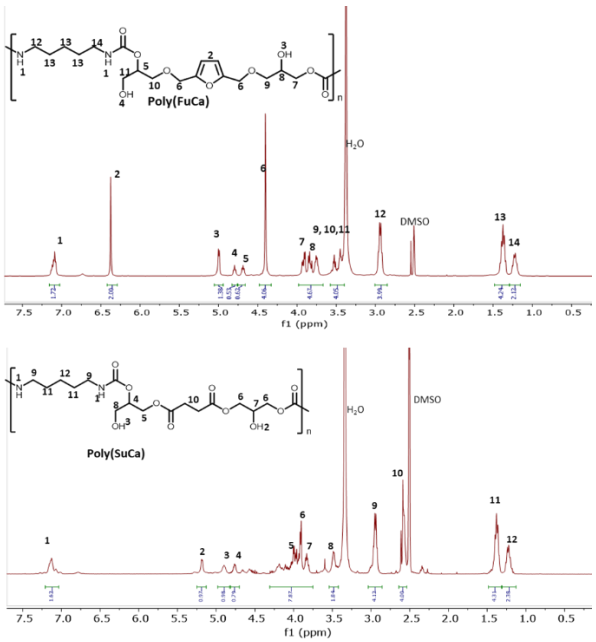


Figure 2. $^1$H NMR of the biobased NIPUs

To the best of our knowledge the application of this methodology for functionalization of synthetic polymers is not explored so far. During the phosphorylation of NIPUs, a significant challenge arose due to their poor solubility except in polar solvents like DMF at ambient conditions. The phosphorylation of poly(FuCa) and poly(SuCa) was thus initially carried out (for screening purpose) in DMF as the solvent at room temperature. Accordingly, 15±5% and 50±5% phosphate functionalization was achieved using 0.4 and 2.2 equivalents of

TBAP respectively relative to the NIPUs forming the corresponding phosphate monoesters as shown in Scheme 1. The amount of TCAN employed was 1.1 to 1.5 equivalent to TBAP. In an effort to find more environmentally friendly solvents for this step, further solvent evaluations were performed at slightly elevated temperatures and it was found that poly(FuCa) and poly(SuCa) were soluble in GVL, a biomass derived fully degradable and non-toxic green solvent,[69] at 50°C. Finally, phosphorylation reactions of all these polymers were carried out in GVL as the primary solvent at 50°C to produce phosphate containing NIPUs for further evaluation.

The degree of incorporation of phosphate in poly(Fuca)-P15 and poly(Fuca)-P50 was estimated by $^{1}$H NMR (Figure 3) using the ratio of integrations of the heterocyclic furan proton at 6.37 ppm and the terminal methyl groups of the tetarbutylammonium counterion at 0.94 ppm. Similarly, for the determination of degree of functionalization in poly(SuCa)-P15 and poly(SuCa)-P50 the ratio of integrations of alpha methylene protons of urethane NH at 2.95 ppm and tetarbutylammonium counterion at 0.94 ppm were used. $^{31}$P NMR spectra of these functionalized polymers showed signals between 2 to -9.5 ppm indicating the presence of phosphate monoesters (Figures S9-S12). The peaks found within the range of 2 to -1 ppm correspond to monophosphates, while those within the range of -8 to -9.5 ppm may indicate diphosphates.[79] Size exclusion chromatography (SEC) of the NIPU phosphate mono esters in 0.1 N $NaNO_3$ solution using polyethylene oxide (PEO) calibration showed average molecular weights (Mn) in the range of 1000-5000 Da. The lower molecular weight observed in SEC could be likely due to higher polymer-SEC column interaction of these polar and ionic phosphate polymers besides the non-ionic calibration standard (PEO) used. The DSC analysis of poly(FuCa)-P15 and poly(FuCa)-P50 revealed higher glass transition temperatures (Tg) of 21 °C and 20 °C, respectively, compared to the unmodified poly(FuCa) with a Tg of 8 °C. Similarly, poly(SuCa)-P15 and poly(SuCa)-P50 also exhibited elevated Tgs of 8 °C and 4 °C, respectively, in contrast to the unfunctionalized poly(SuCa) with a Tg of -6 °C, though, the values were slightly lower than their corresponding furan-containing counterparts. The TGA analysis of the phosphate functionalized NIPU polymers demonstrated their stability up to 148 °C in air. Although there was a drop in $T_{5\%}$ compared to the parent NIPUs, all samples remained stable. Specifically, poly(FuCa)-P15 and poly(FuCa)-P50 exhibited $T_{5\%}$ values of 183 °C and 148 °C, while poly(SuCa)-P15 and poly(SuCa)-P50 showed $T_{5\%}$ values of 189 °C and 165 °C, respectively.

The *E* factor[64] of individual steps such as synthesis of biobased biscarbonate monomers, biobased NIPUs and NIPU-phosphate monoesters were calculated as given in Scheme 1 (details in SI). The E factor values range from 6 to 27, which falls within the accepted range of fine chemicals synthesis.[64] Further improvement is possible by optimising the reaction conditions and purification steps by solvent reduction and recycling.

**Solubility and emulsifying properties of NIPU phosphate monoesters**

The NIPU phosphate monoesters synthesized exhibited water solubility or dispersibility, as well as compatibility with ethanol, dipropylene glycol, and ethoxydiglycol, which are commonly used solvents in the personal care and cosmetic industry. These properties were observed even without the need for any external surfactants, as indicated in Table 4. Interestingly, poly(FuCa)-P15, poly(SuCa)-P15, and poly(SuCa)-P50 formed stable dispersions in water at 10wt% solid loading, with zeta potentials of -55 mV, -49 mV, and -31 mV, respectively, at 25°C. poly(Fuca)-P50 was fully soluble in all these solvents under the specified conditions (Table 3). Furthermore, viscosity of aqueous solutions of poly(FuCa)-P50 was measured at different solid loadings (10wt%, 30wt%, and 50wt%), resulting in viscosity values of 1.83±0.04, 14.84±0.04, and 164.07±0.39 mPa·s, respectively. Notably, this NIPU phosphate monoester exhibited low to moderate viscosity even at high solid loadings, making it particularly appealing for specific personal care applications, such as being used as an ingredient in spray formulations.

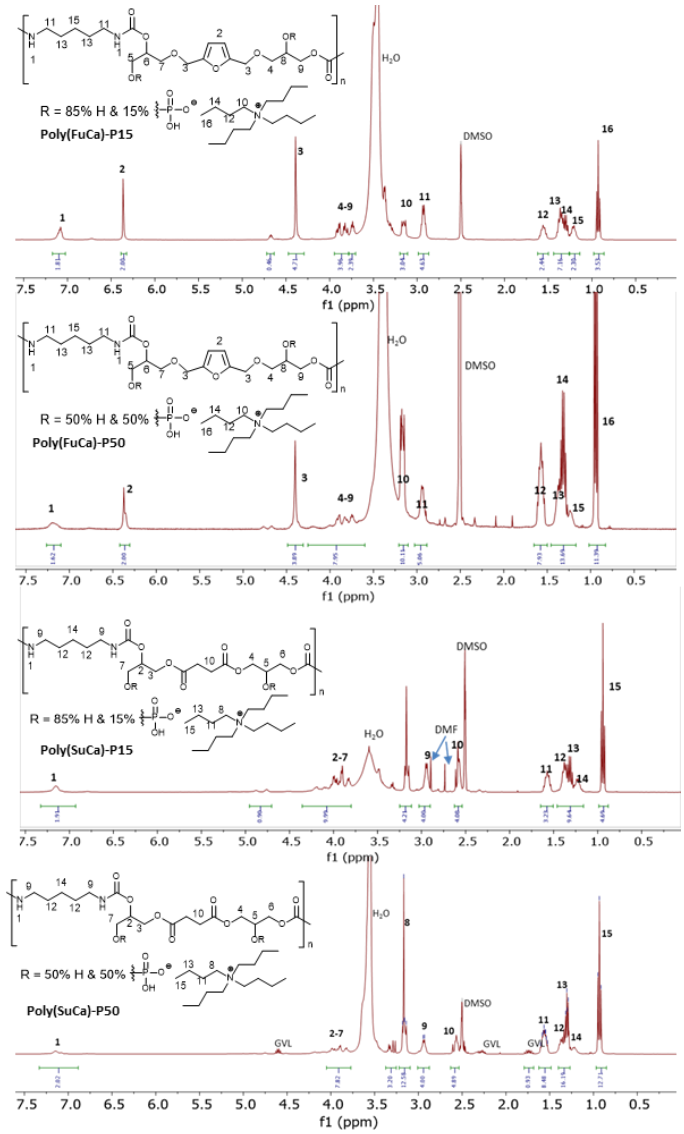


Figure 3. $^{1}$H NMR of the biobased NIPU phosphate monoesters

Table 4. Solubility/dispersibility of NIPU phosphate monoesters in different solvents

| Polymer | Solubility [a] | | | |
|---|---|---|---|---|
| | Water | Ethanol | Ethoxy diglycol | Dipropylene glycol |
| Poly(FuCa)-P15 | SD (-55 mV) | PS | Partial | Partial |
| Poly(FuCa)-P50 | FS | FS | FS | FS |
| Poly(SuCa)-P15 | SD (-49 mV) | PS | FS | FS |
| Poly(SuCa)-P50 | SD (-31 mV) | FS | FS | FS |

[a] The solubility of polymers was assessed by dissolving 10wt% of the polymer in the solvent at 25 °C. FS = Fully soluble and clear solution, PS= Partially soluble, SD=stable dispersion and zeta potential in parenthesis

Apart from their aqueous dispersibility and solubility, the NIPU phosphate monoesters, which consist of a hydrophobic backbone and hydrophilic phosphate pendants, were tested for their potential as secondary emulsion stabilizers or surfactants for hydrophobic oils in water. Branched polymers with a hydrophobic backbone and hydrophilic side chains are well-known for their effective stabilization of oil-in-water (o/w) emulsions due to steric hindrance and multipoint anchoring at the oil-water interface.[80] In this study, olive oil was selected as the oil phase for the initial assessment. The o/w emulsions were prepared with a 10:90 oil-to-water ratio and 0.5 wt% of the polymer. Encouragingly, poly(Fuca)-P50 and poly(SuCa)-P15 showed well-defined o/w emulsions with droplet sizes below 5-20 µm, as shown in Figure 4. In the absence of the polymer additive, clear visible separation of the oil phases occurred, and the slightly turbid water phase contains irregular bigger droplets of oil as seen in Figure S31 in SI. Although in the early stage, these observations suggest that NIPU phosphate monoesters have the potential to function as effective emulsion stabilizers.

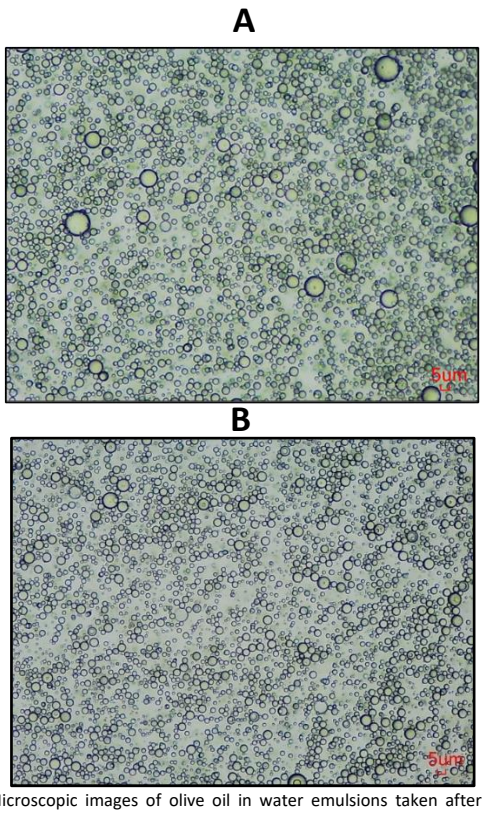


Figure 4. Microscopic images of olive oil in water emulsions taken after leaving the emulsions for 24 h A) Poly(FuCa)-P50 B) Poly(SuCa)-P15

**Antimicrobial activity of NIPU phosphate monoesters**

The antimicrobial activity of small molecule phosphate monoesters and their salts is well-documented.[81-82] Similarly, polymers containing phosphate groups have been reported to inhibit microbial virulence.[83] We investigated the antimicrobial properties of NIPU phosphate monoesters, specifically poly(FuCa)-P15, poly(Fuca)-P50, and poly(SuCa)-P15, along with their parent NIPU polymers. The NIPU polymers underwent multiple washes with methanol and diethyl ether, and the NIPU phosphate monoesters were reprecipitated three times from methanol using diethyl ether to ensure their purity. The antimicrobial tests were conducted using a gram-negative bacteria (*E. coli*) and a gram-positive bacteria (*Bacillus*). As

depicted in Figure 5, the NIPU phosphate monoesters exhibited significant antimicrobial activity (higher zone of inhibition as represented by the red circle in Figure 5) compared to their unmodified linear NIPU polymers against both gram-positive and gram-negative bacteria. Particularly, poly(FuCa)-P50 displayed significantly higher zone of inhibitions, measuring 21.7 mm and 24.8 mm against *Bacillus* and *E. coli*, respectively, compared to poly(Fuca)-P15, which exhibited zone of inhibitions of 17.2 mm and 21 mm against the same bacteria. In contrast, poly(Fuca) showed no inhibitory effect against either *Bacillus* or *E. coli*. Similarly, for poly(SuCa)-P15, the zone of inhibitions against *Bacillus* and *E. coli* were 17 mm and 21 mm, respectively, whereas poly(SuCa) did not exhibit any inhibitory effect against *Bacillus*, though a zone of inhibition measuring 17 mm was observed against *E. coli*. DMSO solvent was used as control which showed no inhibition in both the cases. The observed antimicrobial activity of these NIPU phosphate monoesters could be attributed to the combined effects of the phosphate and tetrabutylammonium cation functionalities.[82,84]

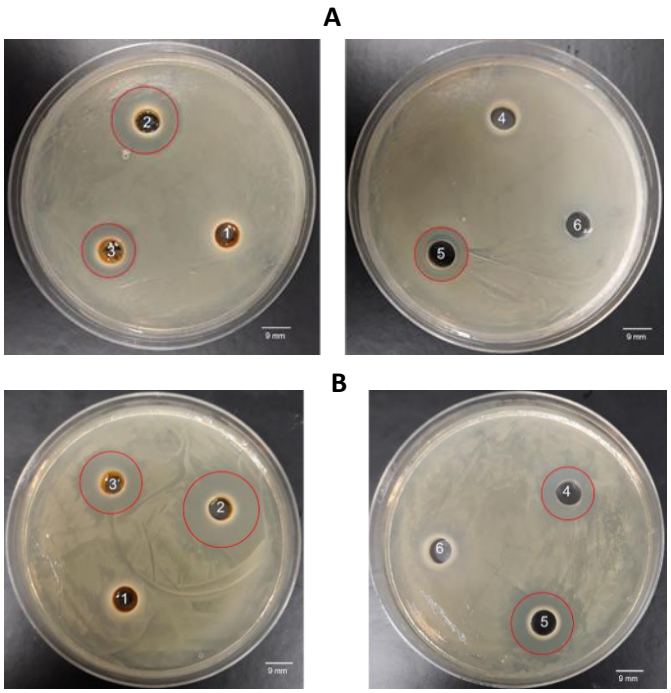


Figure 5. Microbial growth inhibition of NIPU phosphate monoesters against microorganisms (petri dish diameter 90mm). The zones of inhibition are shown by red circles. A) Activity on *Bacillus*. **1** = Poly(FuCa) (d = 0.0 mm); **2** = Poly(FuCa)-P50 (d = 21.7 mm); **3** = Poly(FuCa)-P15 (d = 17.2 mm) **4** = Poly(SuCa) (d = 0.0 mm); **5** = Poly(SuCa)-P15 (d = 17.2 mm); **6** = DMSO (d = 0.0 mm) ; B) Activity on *E. coli*. **1** = Poly(FuCa) (d = 0.0 mm); **2** = Poly(FuCa)-P50 (d = 24.8 mm); **3** = Poly(FuCa)-P15 (d = 21 mm); **4** = Poly(SuCa) (d = 17.2 mm); **5** = Poly(SuCa)-P15 (d = 21 mm); **6** = DMSO (d = 0.0 mm)

### Invitro skin irritation and cytotoxicity evaluation of NIPU phosphate monoesters

Besides thermal and physical properties, understanding the toxicity of NIPU phosphate monoesters is crucial, especially when considering their potential applications in the personal care and cosmetic industries. Remarkably, in the evaluation of their cytotoxicity using human keratinocyte HaCaT cells,[86-87] these phosphate-functionalized polymers exhibited minimal or no growth inhibition up to 1 mg/mL concentration (Figure 6A). Furthermore, when subjected to OECD TG 439 in vitro skin irritation assay using reconstructed human epidermis (EpiSkin), poly(FuCa)-P50 was found to be non-irritant (Figure 6B). These initial in vitro studies suggested that the NIPU phosphate monoesters might possess non-cytotoxic and non-skin irritant properties. However, for a comprehensive understanding of their toxicity profile in real-life circumstances further detailed in vitro and in vivo studies would be necessary.

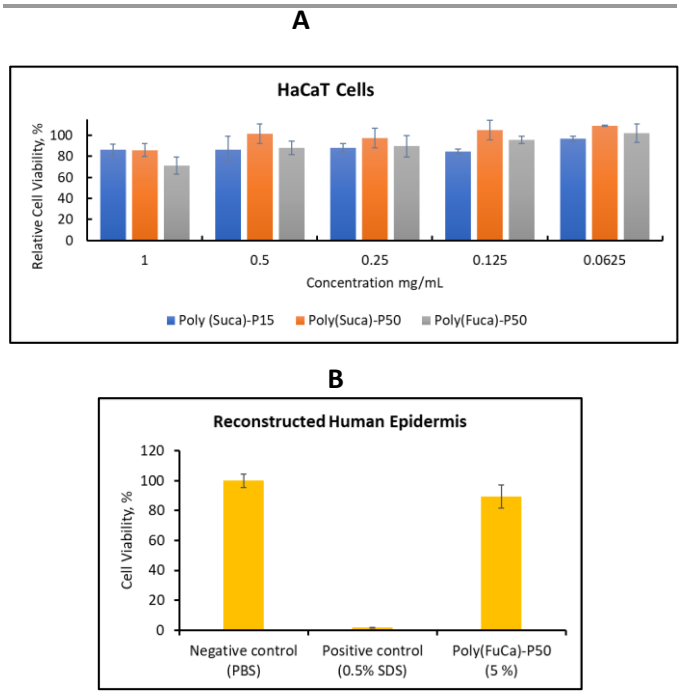


Figure 6. A) Cell viability results for cytotoxicity and B) in vitro skin irritation tests of NIPU phosphate monoesters

### Biodegradation of NIPU phosphate monoesters

Assessing the biodegradability of water-soluble NIPU phosphate monoesters was also essential, given that these polymer additives might eventually end up in wastewater when utilized in personal care and cosmetic applications. Hence, we conducted biodegradability tests on the water-soluble NIPU phosphate monoesters, poly(FuCa)-P50 and poly(SuCa)-P50, using the Zahn Wellens OECD-302-B method with activated sludge extracted from the Jurong water reclamation plant in Singapore. Remarkably, the results indicated that poly(FuCa)-P50 and poly(SuCa)-P50 exhibited approximately 75% and 56% biodegradability, respectively, within a 28-day period. As a positive control, ethylene glycol demonstrated close to 80% biodegradability. These findings are highly promising, particularly considering that there are only limited studies[50-51] on water soluble and biodegradable NIPUs. The biodegradability of these NIPU phosphates might be facilitated by their water solubility and the presence of easily hydrolysable functionalities such as phosphate, urethane, and ester. These

functional groups can be broken down by extracellular enzymes like phosphatases, esterases, and aminopeptidases, which are produced by common bacteria found in activated sludge.[85] Consequently, the simpler soluble compounds released can undergo further metabolism by microorganisms, thus promoting the biodegradation process.

## Conclusions

In conclusion, we have demonstrated a scalable and environmentally friendly synthetic method[62] for novel water-soluble/dispersible phosphorus-containing nonisocyanate polyurethanes (NIPU phosphate monoesters). These NIPUs were synthesized from readily available bio-derived platform chemicals, including 2,5-dihydroxymethylfuran (DHMF), succinic acid, 1,5-pentanediamine (Cadaverine), glycerol carbonate, and $CO_2$. The linear NIPU polymers, poly(FuCa) and poly(SuCa), were obtained through the polymerization of cyclic biscarbonates, FuBCC and SuBCC with 1,5-pentanediamine (Cadaverine). Subsequently, the resulting NIPUs were functionalized through mild and selective phosphorylation, using tetrabutylammonium dihydrogenphosphate as the phosphate source resulting in the production of NIPU phosphate monoesters comprising up to 50% phosphate content which exhibited the following characteristics: 1) water solubility/dispersibility. 2) Inherent aerobic biodegradability, with degradation ranging from 56% to 75% within 28 days. 3) Non-toxicity, showing minimal to no growth inhibition of human keratinocyte HaCaT cells at concentrations up to 0.5 mg/mL. 4) Non-skin irritation, as determined by an in vitro skin irritation assay using reconstructed human epidermis. 5) Effective oil-in-water emulsion stabilization. 6) Antimicrobial activity against *E. coli*, (gram-negative) and *Bacillius* (gram-positive). To the best of our knowledge, this is the first report on phosphate containing nonisocyanate polyurethanes. The syntheses and characteristics of these functional polymers fulfils at least 9 of the 12 green chemistry principles[63] such as incorporating less hazardous chemistry, atom-economic synthesis, and the use of renewable feedstock. The *E* factor[64] of individual synthesis steps ranges from 6-27, which falls within the accepted range of fine chemicals synthesis.[64] This work emphasizes potential suitability of these biobased, non-toxic and biodegradable nonisocyanate polyurethane phosphate monoesters as versatile multifunctional ingredients in personal care and cosmetic products.

## Author Contributions

Conceptualization, funding acquisition and project administration, J. S., A.M.S., and S.J ; methodology, J.S., E.K.W.T., B.S., and P.S.C.; investigation, E.K.W.T., N.X.C, B.S., and P.S.C.; formal analysis, J.S., E.K.W.T., N.X.C and P.S. C.; writing—original draft preparation, J.S., E.K.W.T., and N.X.C.; writing—review and editing, J.S., A.M.S., S.J., E.K.W.T., B.S. and P.S.C.; All authors have read and agreed to the published version of the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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